Kinetic Mechanisms Determining Variability in Low Density Lipoprotein Levels and Rise with Age

Scott M. Grundy, Gloria Lena Vega, and David W. Bilheimer

Levels of plasma low density lipoproteins (LDL) vary among individuals at any given age and frequently rise with increasing age. Both production rates and fractional clearance rates (FCRs) of LDL theoretically could affect the plasma levels of LDL. To evaluate the relative importance of these two factors, turnover rates of LDL apoprotein (apoLDL) were determined in two groups: 1) 19 young adult men aged 23 to 29 years and 2) 15 middle-aged men aged 40 to 60 years. Results were compared to a group of six healthy young adults (aged 22 to 28 years) who we previously studied and who were on a cholesterol-lowering diet. In both groups in the current study, a diet resembling the average American diet was consumed, and LDL levels ranged from low-to-high normal. On average, the 19 young adult men had lower levels of total cholesterol and LDL cholesterol than did the middle-aged men. The younger men also had significantly higher FCRs and lower production rates of apoLDL. When data from all subjects were pooled, apoLDL levels were negatively and significantly correlated with FCRs and positively and significantly correlated with production rates. Similar relations were found with LDL cholesterol levels. These results show that both FCRs and production rates of apoLDL are important regulators of plasma LDL levels; the correlation suggests that the FCR is more influential at lower LDL concentrations, and that production rates are more influential at higher LDL concentrations.

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Since even mild-to-moderate elevations of plasma low density lipoproteins (LDL) are associated with increased risk for coronary heart disease (CHD), a better understanding of factors regulating plasma levels of this lipoprotein is needed. Even within a relatively homogenous population there is considerable variability in levels of LDL, and for the American population as a whole, the average level rises with age. Both dietary and genetic factors have been implicated in this variability, but except for uncommon families with a defect or absence of LDL receptors, the metabolic regulation of LDL levels is poorly understood.

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In general terms, concentrations of LDL must be determined by the balance between rates of input and fractional clearance of this lipoprotein from plasma. LDL is derived from the catabolism of very low density lipoproteins (VLDL). Lipolysis of VLDL triglycerides produces VLDL remnants, or intermediate density lipoproteins (IDL), and these in turn are either cleared by the liver or converted to LDL. The quantity of VLDL converted to LDL thus appears to determine the production of LDL. The clearance of plasma LDL can occur by two pathways: the major path normally is via specific cell-surface receptors for LDL in many tissues, and the lesser pathway is by nonspecific uptake of LDL. Recent evidence indicates that LDL receptors also mediate the removal of circulating VLDL remnants, or IDL, from the plasma.

As a step toward understanding the importance of these pathways in regulating LDL levels in humans, we examined the relative roles of production rates and fractional clearance rates of LDL in determining the variability in LDL levels within specific age ranges and between different age groups. For this purpose, turnover rates of LDL were measured in two groups of normal men: young-adult men whose
LDL levels ranged from low to high normal for their age group and middle-aged men whose LDL levels were normal for their age but generally were higher than those of the young adult men. Our results indicate that both production rates and fractional clearance rates of LDL contribute to variability of LDL levels in both age groups, and that changes in both are responsible for the higher LDL levels in the older men.

Methods

Patients

Nineteen young men (mean age 24.9 ± 0.5 years, sem, range 23 to 29 years) volunteered for this study. All subjects were healthy; none were obese (the percent of ideal body weight, %IBW, averaged 102% ± 2%). Plasma cholesterol concentrations for all subjects were normal for their age and sex.6,7 We selected subjects with LDL levels ranging from low to high normal, with a group mean near the 50th percentile for their age and sex.6,7

The studies were conducted in the General Clinical Research Center of Parkland Memorial Hospital, Dallas, Texas. Included in this report are the results for six other young adults (three men and three women, mean age 26 ± 1 years and mean %IBW, 109% ± 3%). These subjects also were studied in the research center of Parkland Memorial Hospital, and their results have been previously reported.8

The results in our young adults were compared with those of 16 middle-aged men (mean age 55.6 ± 8.3 years, range 40 to 60 years, and 109% ± 3% %IBW). Seven of the middle-aged men were studied in either the research center or the metabolic unit at the Veterans Administration (VA) Medical Center, Dallas, Texas. The other eight were studied under similar conditions at the VA Medical Center, San Diego, California; data from these latter patients have been reported previously.8

The studies were approved by the appropriate institutional review boards, and all subjects gave informed consent for participation in the studies.

Experimental Design

The 19 young men were selected for study after measurement of their fasting plasma lipids while they consumed their usual diets. Upon entrance into the study, they were started on a solid-food diet consisting of 40% of calories as fat (18% saturates, 17% monounsaturates, and 5% polyunsaturates), 45% as carbohydrate, and 15% as protein. Dietary cholesterol was approximately 150 mg per 1000 calories. Subjects were given a repetitive menu to follow as closely as possible, and they were counseled on food preparation and serving sizes. Under this protocol, the weight and plasma lipids of the subjects did not fluctuate significantly during the study period. The subjects were admitted to the research center for 36 hours to initiate the LDL turnover, and thereafter, they continued their studies as outpatients. Fasting blood samples were taken each morning in the center.

The seven middle-aged men studied in Dallas followed an identical protocol, while the eight men studied in San Diego consumed a similar diet;9 in the latter, however, turnover rates of LDL were measured entirely in the metabolic ward. The six young subjects reported previously9 also were hospitalized throughout their study, but their diet was different and contained more polyunsaturated fatty acids (P/S ratio = 1.5) than the diet of subjects of the present study (P/S ratio = 0.28); dietary intakes of cholesterol in the previous young adults averaged 300 mg per day.

Two weeks after beginning the experimental diet, the LDL turnover studies were begun. The studies were performed as described previously9 with analogous LDL (d = 1.019–1.063 g/ml) isolated by ultracentrifugation in fixed-angle rotors. Lipid and lipoprotein measurements were performed as described previously8 except that all cholesterol measurements were performed by gas-liquid chromatography.10 ApoLDL was labeled with 125I, the labeled lipoprotein was injected into patients, and blood samples were obtained daily for 20 days thereafter. Parameters of apoLDL turnover were calculated by using a two-pool model;11 these included fractional clearance rates (FCRs) and transport rates for apoLDL. The term "production" of apoLDL will be used synonymously with "transport."

Comparisons of means and linear regression analysis were done by standard linear statistical procedures with use of a DEC 10 computer. Nonlinear regression analysis was performed by nonlinear statistical programs (SAS).

Results

Concentrations of plasma total cholesterol (TC), triglycerides (TG), lipoprotein cholesterol, and kinetic parameters of apoLDL in the young men in this study are shown in Table 1. Values obtained previously for the six young adults8 and the average plasma concentrations for men aged 20 to 29 years in the Lipid Research Clinic (LRC) Prevalence Study6,7 are presented for comparison. The average levels of TC, TG, LDL-C, and HDL-C in the young adults of our study were similar to the overall mean levels of the LRC survey. Compared to previously studied subjects on a cholesterol-lowering diet,8 the men of our study had significantly higher levels of LDL-C, apoLDL, and production rates of apoLDL; although the mean FCR was lower in this study group, the difference was not statistically significant. For the young men in this study, concentrations of apoLDL were linearly and negatively correlated with FCRs (r = 0.59, p < 0.008); concentrations were also linearly and positively correlated with transport rates (r = 0.71, p < 0.002). Likewise, LDL-C levels...
Table 1. Plasma Lipids, Lipoproteins, and LDL Kinetics in Young and Middle-Aged Men

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Current young men</th>
<th>Middle-aged men</th>
<th>Apo-LDL</th>
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<td>TC (mg/dl)</td>
<td>TG (mg/dl)</td>
<td>LDL-C (mg/dl)</td>
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<td>Previous young subjects (n = 6)†</td>
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<tr>
<td>± SD</td>
<td>±16</td>
<td>±32</td>
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Mean values for men aged 20-29 years and for men aged 40-59 years of the Lipid Research Clinic (LRC) Population Survey (see references 6 and 7).
†Patients reported previously in reference 8.
‡Patients reported previously in reference 9.
§Values for middle-aged men are significantly different from those for current young men (p < 0.02, Students' t test).
TC = total cholesterol; TG = triglyceride; FCR = fractional clearance rate.
correlated negatively with the FCRs for apoLDL \( (r = -0.71, p < 0.001) \), and positively correlated with transport rates of apoLDL \( (r = 0.51, p < 0.05) \).

The results for the 15 middle-aged men (Table 1) are compared to the means of the LRC survey for men 40 to 59 years of age. Levels for all plasma components were similar between the two groups. Compared to the young men in our study, levels of LDL-C and apoLDL were significantly higher in middle-aged men; transport rates of apoLDL also were higher in the latter, and their FCRs were significantly lower. For the middle-aged men, apoLDL levels correlated negatively with the FCRs \( (r = 0.51, p < 0.05) \) and positively with transport rates \( (r = 0.60, p < 0.02) \); plasma LDL-C also correlated negatively with FCRs for apoLDL \( (r = -0.61, p < 0.02) \), but not with transport rates \( (r = 0.094) \).

The data of LDL kinetics from all groups were combined and examined for correlations. For all subjects, levels and FCRs of apoLDL were negatively correlated \( (Y = 2.55X^{0.47}; r = 0.72, p < 0.005) \); the curve was steepest at low levels of apoLDL, and it tended to flatten at higher levels. In contrast, a positive correlation was observed between concentrations and production rates for apoLDL. The best-fit function for production rates were exponential \( [Y = 5.56 \exp(0.01)X; r = 0.80, p < 0.005] \); the steepness of the curve increased at higher apoLDL levels. Similar relations were noted between concentrations of LDL-C and both FCRs and production rates of apoLDL (Figure 2).

Discussion

Our objectives were twofold: 1) to determine factors regulating plasma LDL levels over a broad range of concentrations from low to high within defined age groups, and 2) to determine the causes of the rise in LDL levels with age. The two groups under investigation — young adult men and middle-aged men — were not recruited as a random population sample and hence their representativeness cannot be assumed. However, the distribution of LDL-C levels was comparable to that of American men of their age groups. In this section, we will consider the kinetic parameters affecting concentrations of LDL and discuss the role of fractional clearance rates (FCRs) for apoLDL separate from the contribution of production rates of LDL.

**Fractional Clearance of LDL**

For young adult men, when concentrations of LDL-C were in the lower ranges, FCRs for apoLDL were relatively high. At higher concentrations, but still
REGULATION OF LDL LEVELS  Grundy et al.  627

within the normal range, FCRs were distinctly lower. These young adults thus had a highly significant and negative correlation between FCRs for apoLDL and concentrations of both apoLDL and LDL-C. The FCR for apoLDL varied considerably from one individual to another, and it was inversely related to the level of LDL.

Several previous studies have measured the FCRs for apoLDL in healthy young adults. In three such studies, diets rich in polyunsaturated fatty acids were consumed, and concentrations of LDL-C were relatively low. For example, Langer et al.12 measured FCRs for apoLDL in six young men (aged 23 ± 2 years old); the fat of their diet had a P/S ratio of 2.5; the plasma LDL-C levels in these men were relatively low (mean = 98 ± 4 mg/dl), and their mean FCR for apoLDL was high (mean = 0.47 ± 0.09 pools/day). Similar results were obtained by Bilheimer et al.14 in six young adults who also were given a diet high in polyunsaturates (P/S 1.5); the mean concentration LDL-C of this group was even lower (76 ± 5 mg/dl), and FCRs for apoLDL averaged 0.45 ± 0.07 pools/day. In a third study, Garnick et al.13 determined turnover rates of apoLDL in six young adults (mean age 27 ± 3 years) who received a P/S ratio of 2.7; their mean plasma LDL-C was 111 ± 7 mg/dl, and FCRs for apoLDL averaged 0.41 ± 0.02 pools/day. In these reports, levels of LDL-C usually were near or below the 50th percentile for age,6,7 and FCRs for apoLDL frequently were over 0.40 pools/day. In contrast, Shepherd et al.14 measured LDL kinetics in eight young men fed a diet high in saturated fatty acids. Compared to subjects in previous studies that used a high P/S ratio,6,12,13 the subjects in Shepherd et al.'s study had a mean level of LDL-C that was considerably higher (134 ± 24 mg/dl); in accord, the mean FCR for apoLDL in this group was much lower (0.32 ± 0.04 pools/day).

Although these four studies clearly show that FCRs for apoLDL are inversely correlated with levels of LDL-C, they were not designed to delineate the range for FCRs associated with normal concentrations of LDL-C in young adults ingesting a diet resembling the composition of the average American diet. To achieve this aim, we fed the latter diet to young men whose levels of LDL-C covered the “normal” range, i.e., from the 5th to 95th percentile, with a mean at the 50th percentile for their age group.6,7 Although several of these men had relatively high FCRs, most had FCRs below 0.35 pools/day, and in some, they were below 0.30 pools/day. Thus, FCRs for apoLDL in young men consuming an average American diet apparently are lower than noted previously for subjects of the same age ingesting diets high in polyunsaturates. Nonetheless, our results leave little doubt that the FCR for apoLDL is correlated significantly with concentrations of LDL-C in this age group during ingestion of a typical American diet.

The middle-aged men of this study had distinctly higher levels of LDL-C than did younger men (144 ± 23 vs 108 ± mg/dl, respectively). Still, the average LDL-C level for the middle-aged group was near the 50th percentile for their age and sex.6,7 Recently, Miller15 has posed the question of why plasma concentrations of LDL-C rise with age. He reviewed data from 22 reports in which turnover rates of LDL were estimated in subjects of differing age and disease status; he concluded that the rise in LDL-C with age is due almost entirely to a reduction in the FCR for apoLDL. In our study, the mean FCR was significantly lower in the middle-aged group than in the younger group; this finding is consistent with Miller’s conclusion, at least to the extent that a lower FCR is one factor associated with the rise in LDL levels with age.

The FCRs for apoLDL also were correlated with levels of LDL-C for our 16 middle-aged men. Kesan- iemi and Grundy9 previously noted that FCRs for apoLDL were not significantly correlated with LDL-C levels in middle-aged men, but in their study, concentrations of LDL-C on the average were higher than those of current patients (171 ± 33 vs 144 ± 108 mg/dl); and as shown in Figure 2, the relation between concentrations and FCRs becomes essentially flat at the higher levels of LDL-C. This latter phenomenon also was reported by Turner et al.16 for men of intermediate age (35 to 49 years). For their subjects who had LDL-C levels in the lower tertile (mean LDL-C = 108 ± 15 SD mg/dl), the FCRs for apoLDL were relatively high, but the mean FCRs were not different between those of the middle and upper tertiles (mean LDL-C = 162 ± 10 and 204 ± 34 mg/dl, respectively). In this study, the FCRs for apoLDL flattened out at a mean of about 0.30 pools/day, similar to our own findings (Figure 1).

Production Rates of ApoLDL

Another factor correlating with concentrations of apoLDL and LDL-C in our young men was the production rate of apoLDL. The same was true for middle-aged men. As shown in Figures 1 and 2, production rates of apoLDL were positively correlated with concentrations of apoLDL and LDL-C, and the correlation became steeper with rising concentrations. Thus, in middle-aged men who had higher concentrations of LDL-C, the production rates of apoLDL became the predominant influence on concentrations of LDL. A significant correlation between production rates and concentrations at the higher levels of LDL also was reported previously by Kesaniami and Grundy9 and Turner et al.15 Although the analysis carried out by Miller15 suggested that production rates are not a significant cause of the rise of LDL levels with age, the current results indicate that they are. The middle-aged men as a group had significantly higher production rates of apoLDL than did younger men.

Factors Influencing Kinetic Parameters of LDL

The FCR for apoLDL seemingly reflects two processes responsible for catabolism of LDL, namely,
clearance of LDL by receptor-mediated and nonreceptor-mediated pathways. The importance of LDL receptors in the regulation of LDL clearance is revealed by the elevated levels of LDL in patients with familial hypercholesterolemia, a condition in which LDL receptors are absent or defective. Patients with the heterozygous form of this disease have inherited a defective gene from one parent and thus have only one-half the normal number of LDL receptors; their FCRs for apoLDL are low and their levels of LDL-C are high. In rare patients who inherit the defect from both parents, LDL receptors are essentially absent, and LDL-C levels are extremely high. In such patients with homozygous familial hypercholesterolemia, the FCR for apoLDL is extremely low, about 0.15 pools/day. This latter FCR reflects the clearance capacity of the nonreceptor pathway; that this is so has been confirmed by the finding that LDL that has been chemically modified to block receptor-mediated clearance has an FCR of approximately 0.15 pools/day in normal people. Theoretically therefore, when the FCR is 0.30 pools/day, catabolism of LDL should be distributed equally between receptor and nonreceptor pathways, and when the FCR is 0.45 pools/day, approximately two-thirds of the LDL is removed by the receptor pathway. Thus, the variable portion of the FCR appears to be determined by the activity of LDL receptors. This conclusion is in accord with the recent data of Turner et al. which showed a direct relationship between the FCR of apoLDL measured in vivo and the rate of receptor-mediated catabolism of LDL by mononuclear cells in vitro.

If the variability in FCRs in our subjects was due to differences in LDL-receptor activity in vivo, then both environmental and genetic factors could have influenced this activity. In this study, however, we attempted to control for the major environmental factor, namely, diet. We therefore assume that the observed variability in FCRs was a function more of genetic influence than of environmental impact. Genetic factors might affect LDL-receptor activity in at least three ways: 1) by affecting the number of LDL receptors synthesized; 2) by influencing the affinity of the receptor for LDL; and 3) by affecting the affinity of LDL for the receptor. To date, differences in binding properties of the receptor for LDL have not been described, and in our view, the genetic factor most likely to explain the variability in LDL-receptor activity is an inherited control of LDL-receptor synthesis. Indeed, Weight et al. have reported that the maximal activity of LDL receptors in peripheral cells (i.e., blood mononuclear cells) is variable and largely genetically determined.

Variability in FCRs for apoLDL theoretically could be due to differences in the affinity of LDL for LDL receptors. Differences in affinity might be caused either by individual differences in the apo B molecule that affect its binding to receptors or by differences in overall composition of LDL particles. Not only might such differences exist among individuals in the same age group, but with aging the composition of LDL may change in a way that influences its binding to LDL receptors. There is evidence for increasing heterogeneity of LDL with age, which might give rise to multiple functional pools within the LDL compartment.

Miller has postulated that a decline in FCRs for apoLDL with increasing age probably reflects a decrease in activity of LDL receptors. This fall in activity might be due to "aging" in general, or it could be of dietary origin. Several studies suggest that saturated fatty acids, compared to polyunsaturated fatty acids, reduce the FCR of apoLDL; furthermore, Packard et al. have shown that dietary cholesterol decreases the FCR of apoLDL. Thus, both dietary cholesterol and saturated fatty acids probably suppress the activity of LDL receptors, as documented recently in experimental animals by Spady and Dietzchy. For this reason, a prolonged intake of a diet rich in cholesterol and saturated fatty acids could accentuate the suppression of LDL-receptor activity. In other words, the immediate action of saturated fatty acids and cholesterol to lower the FCR and raise concentrations of LDL may give way to a greater longer-term effect that further raises LDL levels. Such might occur, for example, from a gradual increase in body stores of cholesterol with aging. Evidence that the body does not lose the capacity to produce LDL receptors with aging comes from the finding of Bilheimer et al. that maximal-induced activity of LDL receptors in peripheral blood lymphocytes does not decline with age.

Another factor that might contribute to differences in FCRs of apoLDL among individuals could be variable binding of LDL to receptors as a function of LDL concentrations. For example, Spady et al. found in experimental animals that when LDL was infused at increasing rates the LDL levels rose and FCRs declined. This suggests a kind of saturation effect. In the current study, a rise in LDL levels was associated with two responses — an increasing production of apoLDL and a declining FCR (Figures 1 and 2). These changes are consistent with a similar saturation phenomenon. Thus, one factor contributing to a reduction in FCR with increasing plasma concentrations of LDL could have been an increasing production rate of apoLDL.

In addition, production rates of apoLDL per se had a significant effect on LDL levels in our study. The two major factors that determine input rates of LDL are: 1) synthetic rates of VLDL and 2) the fractional conversion of VLDL to LDL. Without question, some of the rise of LDL levels with age could be related to increasing rates of VLDL synthesis. An increase in body weight with aging is common, and weight gain may raise the production of VLDL. The higher absolute conversion of VLDL to LDL (i.e., the higher production rate of LDL) in middle-aged men, compared to younger men, could be related to a greater increase above desirable body weight in the middle-age group. An increased synthesis of VLDL also
might be related to a long-term effect of diet composition. For example, Illingworth et al.\textsuperscript{28} reported that administration of fish oils, which are known to inhibit the synthesis of VLDL,\textsuperscript{29} also decrease production of LDL, presumably by making less VLDL available for conversion to LDL.

A second factor determining input of LDL is the fraction of VLDL converted to LDL. Although early kinetic studies\textsuperscript{1} suggested that VLDL normally is converted quantitatively to LDL, more recent investigations\textsuperscript{29} show that this is not true in humans. Some VLDL remnants are removed before conversion to LDL. Furthermore, studies in experimental animals demonstrate that VLDL remnants can be cleared by the liver via LDL receptors.\textsuperscript{3} In other words, not only does the activity of LDL receptors determine rates of clearance of LDL, but it also influences the fractional conversion of VLDL to LDL by removing a portion of the precursors of LDL. Variability in LDL receptor activity thus may account in part for differences in production rates of apoLDL within our two groups of normal men. Indeed, at higher levels of LDL, production rates of apoLDL may be a more sensitive indicator of activity of LDL receptors than the FCR of LDL (Figures 1 and 2). Furthermore, there may be competition between VLDL remnants and LDL for uptake by LDL receptors. Since VLDL remnants probably have a higher affinity for the LDL receptor because of their content of apolipoprotein E,\textsuperscript{31} an enhanced uptake of VLDL remnants through this pathway could curtail uptake of LDL and thus reduce the FCR of the latter.

In summary, this investigation represents an extension of previous studies on LDL metabolism in humans and confirms several reports. The following findings, however, seem to emerge clearly from this work. 1) Both FCRs and production rates of apoLDL are important determinants of LDL concentrations over a broad range of LDL levels. 2) FCRs of apoLDL are most highly correlated with plasma LDL at the lowest concentrations, while the correlation curve tends to flatten at higher levels of LDL. 3) In contrast, the correlation curve between production rates and concentrations is steeper at higher levels of LDL. 4) Changes in both FCRs and production rates of apoLDL, and not merely declining FCRs,\textsuperscript{15} contribute to the rise of LDL levels with age. 5) Parameters of LDL metabolism in young adults and middle-aged men on a typical American diet have been defined; the unusually high FCRs reported previously to be "normal" are shown to be due partly to cholesterol-lowering diets. 6) Genetic factors are strongly implicated as a major cause of variability in LDL levels because of the uniformity of diet during the study. 7) Because of the inclusion of subjects of different ages who had widely differing levels of LDL over the "normal" range, we believe that our results help to reconcile differences reported previously for kinetic parameters of LDL and that these differences were not due merely to differences in laboratory technique. Finally, 8) our results are consistent with the hypothesis that individual differences in the activity of LDL receptors can explain much of the variability in both production rates and FCRs for apoLDL, but that other factors, (i.e., variability in synthetic rates of VLDL, possible "saturation" of LDL receptors, and affinity of VLDL remnants and/or subpopulations of LDL for LDL receptors) also may have contributed to the observed differences.

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References


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